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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/632,657	08/04/2000	Gordon Duff	MSA-012.01	2287

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FOLEY HOAG LLP
PATENT GROUP, WORLD TRADE CENTER WEST
155 SEAPORT BOULEVARD
BOSTON, MA 02110-2600

EXAMINER
MYERS, CARLA J

ART UNIT	PAPER NUMBER
1634	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/632,657	Applicant(s) DUFF ET AL.	
	Examiner Carla Myers	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-12,22-24,43 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-12,22-24,43 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

1. Applicant's election with traverse of group I, claims 1, 5-12, 22-24, 43 and 44 in Paper No. 11 is acknowledged. The traversal is on the ground(s) that the "search for any one of the groups or alleles or nucleic acids would substantially overlap the searches for the others" and thereby would not require an undue search burden. This argument is not convincing because the search for group I is not co-extensive with the search of groups II and III and a search of references teaching an association between IL-RN (+2018) and early onset menopause is not co-extensive with a search of references teaching an association between early onset menopause and an IL-1A, IL-1RN, IL-1B allele or other IL-1 allele or an allele in linkage disequilibrium with said alleles. Applicants comments regarding a restriction between IL-1RN (+2018) allele 1 and IL-1RN (+2018) allele 2 are not understood since the restriction did not require an election of the alleles as specific polymorphic position. The species set forth on pages 5 and 6 of the office action list the alleles recited in the originally presented claims, but does not require the election between different allelic variants at the same polymorphic position. That is, methods of detecting IL-1RN (+2018) allele 1 and allele 2 have been examined herein. Applicants arguments are persuasive regarding treating claims 11, 22, 23 and 43 as linking claims. Accordingly, the restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claims 11, 22, 23 and 43. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or

including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01. Furthermore, Applicants arguments are persuasive regarding the use of primer sets. Accordingly, the primers of SEQ ID NO: 7 and 8 have been examined herein. In summary, claims 11, 22, 23 and 43 have been examined as linking claims, and the remaining claims have been examined with respect to the IL-1RN (+2018) polymorphism and with respect to SEQ ID NO: 7 and 8.

2. The disclosure is objected to because of the following informalities:

In claim 9, a period should be added at the end of the sentence.

3. Claims 1, 5-12, 22-24, 43 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for determining whether an individual of Northern-European descent is predisposed to early onset menopause by detecting the presence of IL-1RN (+2018) allele 2 as indicative of a predisposition to early onset menopause, does not reasonably provide enablement for methods which determine a predisposition to early onset menopause in non-Northern European women by detecting IL-1RN(+2018) allele 2 or methods for detecting early onset menopause by detecting any other IL-1 alleles or haplotypes. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1 and 5-10 are drawn to a method for determining whether a subject is predisposed to having early onset menopause by detecting the presence of an IL-1RN (+2018) allele 2 as predictive of the subject's predisposition to early onset menopause. Claims 11-12 are drawn to a method for determining a subject's susceptibility to early onset menopause by detecting any IL-1 haplotype associated with early onset menopause. Claims 22-24 are drawn to methods for identifying an allelic pattern associated with early onset menopause by identifying a first allele in linkage disequilibrium with a second allele that is associated with early onset menopause. Claims 43 and 44 are drawn to methods for determining a subject's predisposition to early onset menopause by detecting an allele within the 44112332 haplotype.

The specification (pages 60-61) teaches that in women of European descent, the presence of IL-1RN (+2018) allele 2 was found to be associated with early onset menopause. However, in women of non-European descent, the presence of IL-1RN (+2018) allele 2 was found to be associated with **later** onset of menopause, with the effect increasing with each copy of allele 2. Accordingly, the specification has not enabled methods which determine susceptibility to early onset menopause in women of non-European descent by detecting the presence of IL-1RN (+2018) allele 2. Further, the specification does not teach any additional alleles, either IL-1 alleles or non-IL-1 alleles that are associated with early onset menopause. The claims are inclusive of detecting a polymorphism in any gene as indicative of early onset menopause. The

showing of one polymorphism associated with early onset menopause in one ethnic groups is clearly not representative of a genus of all possible polymorphisms in any gene that may be associated with early onset menopause. Extensive, trial and error experimentation would be required to examine additional genes for the presence of a polymorphism associated with early onset menopause. The specification does not provide any guidance as to how to identify any non-IL-1 genes that are associated with early onset menopause without undue experimentation. Regarding the claims as they are limited to methods which diagnose early onset menopause by detecting other IL-1 alleles, the specification does not teach any alleles other than IL-1RN (+2018) which are associated with early onset menopause in women of European descent. While the specification postulates that alleles in linkage disequilibrium with the IL-1RN (+2018) allele 2 could also be used to diagnose early onset menopause, given the fact that other alleles are not in 100% linkage disequilibrium with the stated alleles and that stated alleles have variable frequencies of association with early onset menopause, it is highly unpredictable as to whether alleles in linkage disequilibrium with of IL-1RN (+2018) allele 2 or any other IL-1 allele would be sufficiently correlated with the occurrence of early onset menopause. Further, while the specification suggests that IL-1 genotypes association with inflammation may be used to diagnose any disease that involves inflammation, Applicants have not provided sufficient evidence to establish that any level of inflammation or any inflammatory response in women is correlated with early onset menopause.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation." *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the specification has identified only 1 allele in one IL-1 gene out of all possible IL-1 genes and all possible non-IL-1 genes has exemplified the use of only this one allele (i.e., IL-1RN (+2018) allele 2) as a means for diagnosing a predisposition to early onset menopause Thereby, the scope of the claims does not bear a reasonable correlation to the scope of enablement provided by the specification and undue experimentation would be required to practice the full scope of the claims because this would require randomized searching of IL-1 genes and other genes for additional alleles which may be analyzed for their association with early onset menopause. Additionally, the results set forth in the specification clearly demonstrate the unpredictability in the art since the findings obtained with non-European women were directly opposite of those obtained with European women. The unpredictability in the art of establishing a correlation between a polymorphism and a particular disease is further highlighted by the teachings of Langdahl et al (Journal of Bone and Mineral Research (2000) 15: 402-4140.

Langdahl teaches that linkage disequilibrium between alleles is population dependent and there can be considerable variation between the frequency at which alleles are inherited. The reference also teaches that while one group reported that the repeat polymorphism in the IL-1RN gene was in linkage disequilibrium with the IL-1B (+3954) polymorphism, Langdahl et al were unable to show linkage between these polymorphisms. Again, these teachings demonstrate the unpredictability of using an allele in linkage disequilibrium with a second allele as a means for diagnosing susceptibility to disease. With respect to claims 22-24, the broadest reasonable interpretation of these claims indicates that the claims are inclusive of methods which identify novel alleles associated with early onset menopause. While the specification is enabling for methods for detecting IL-1RN (+2018) allele 2 as indicative of an increase susceptibility to early onset menopause in women of European descent, the specification is not enabling for methods which search for novel alleles that may be in linkage disequilibrium with IL-1RN (+2018) allele 2. To make and use an invention requires that the invention have a "real world" use. However, uses that require carrying out further research do not constitute a real world use. Thus, the specification has not adequately enabled methods which search for novel alleles associated with early onset menopause. Accordingly, in view of the lack of information in the specification as to how to reasonably identify other IL-1 alleles associated with early onset menopause without undue experimentation and in view of the unpredictability in the art in correlating the presence of an allele with a specific condition, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

5. Claims 22-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22-24 are indefinite because the claims are drawn to a method of identifying an allelic pattern, yet the process steps recited in the claim do not result in the identification of an allelic pattern. It is unclear as to how identifying a first allelic pattern that is in linkage disequilibrium with a second allelic pattern results in the identification of an allelic pattern associated with early onset menopause. It is further unclear as to whether the method is one in which an allelic pattern is identified and it may be an inherent property of the allelic pattern that said pattern is associated with early onset menopause, or whether the method is intended to require that one have knowledge of the fact that the allelic pattern is associated with early onset menopause.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper tames extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.d. 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Long*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.32 (c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5-12, 22-24, 43 and 44 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,268,142. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '142 are both inclusive of methods for diagnosing a disease by detecting the presence of IL-1RN (+2018) allele 2 or alleles in linkage disequilibrium with IL-1RN (+2018) allele 2 . The instant claims are limited to methods for diagnosing early onset menopause. The claims of '142 are inclusive of methods for diagnosing any disease associated with a IL-1 inflammatory haplotype. As defined in '142, diseases associated with a IL-1 inflammatory haplotype are inclusive of early onset menopause (column 8).

7. The art made of record and not relied upon is considered pertinent to applicant's disclosure.

Duff et al (WO 98/54359) discloses the concept of determining a patient's susceptibility to an inflammatory disorder by detecting the presence of an IL-1 allele, such as IL-1RN (+2018) allele 2. However, this reference, to which priority is claimed in U.S. Patent 6,268,142, does not specifically teach that the inflammatory disease may be early onset menopause.

Keen et al (reference "DB") teaches that early menopausal bone loss is associated with IL-1RN (+2018) allele 1. Keen does not teach an association between the IL-1RN (+2018) polymorphism and the occurrence of early onset menopause.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

July 25, 2002

CARLA J. MYERS
PRIMARY EXAMINER